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## BIOLOGICAL ENIGMAS AND THE THEORY OF ENZYME ACTION

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### I

DURING the past twenty years the sciences which deal with inorganic physical phenomena have made astounding progress in the logical synthesis of their facts and theories.<sup>1</sup> The beginnings of this synthetic tendency lie, of course, in the middle part of the last century, in the work of such men as Faraday, Maxwell, and Mendelejeff. The discovery of radio-activity by Becquerel in 1896, and the demonstration by Thomson of the electron, in the following year, let loose the pent-up forces of an intellectual avalanche which swept scientific conservatism quite off its feet, and seems to be carrying our thought with thrilling rapidity towards a goal which metaphysical philosophers have for ages regarded with wistful longing. This goal is the comprehension of the physical universe in terms of a few simple conceptions.

The lines of demarcation which once were so rigidly drawn between the departments of physical science are disappearing before our eyes. The discovery of radio-activity, instead of adding a new science to the list, has

<sup>1</sup> D. F. Comstock and the present writer have attempted to give an elementary, but comprehensive presentation of the modern theory of matter in their book, "The Nature of Matter and Electricity," 1917.

brought us very close to a cancellation of all of the names except one; the demonstration of the existence of particles of negative electricity smaller than any known atom, instead of further complicating the facts of chemistry, has introduced a hundred simplifications. Mechanics, chemistry, optics, and the sciences of heat, electricity and magnetism are rapidly fusing into a single logical system, the ultimate terms of which are minute particles of positive and negative electricity, the ultimate laws those of electro-dynamics, and the ultimate problems those of the structures formed by these particles in space and of the changes which these structures undergo in time.

This startling progress in physics during the last two decades has not been the product of unadulterate empirical research. On the contrary, it has been made possible only by acts of daring speculation, which to certain more orthodox scientists of an earlier period might have seemed inexcusably foolhardy. However, their justification has often come so quickly and in such unequivocal terms, that methodological critics have been obliged to remain modestly silent. To indulge in a definite and detailed account of the structure and behavior of single atoms of hydrogen—particles far beyond the visual range of even the ultra-microscope—may seem no more a scientific undertaking than the fabrication of a fairy-tale; and yet when from this account there emerges by inevitable logic a mathematical formula corresponding exactly with the constitution of the complex spectrum of hydrogen, our minds are opened to the possibility that the speculation is pointing the way to a fundamental truth.<sup>2</sup> This impression becomes especially forcible when we consider that the constitution of this same hydrogen spectrum had for twenty-eight years defied the intellects of the best scientists, and by some had been regarded as incapable of explanation upon any simple hypothesis.

It is a fact of fundamental logical significance that the

<sup>2</sup> The reference is to the theory of N. Bohr, published in the *Philosophical Magazine*, 1913, 26; 1, 476 and 857.

progress represented by the modern electro-molecular conception of the physical universe has been achieved by the utilization of *a few general conceptions*, such as those of the electron and electrical action at a distance. These conceptions, although general, *i. e.*, universally applicable, are nevertheless extremely definite. They are also as tangible, or concrete, as it is possible to make them. It is nearly as characteristic of the modern theory of matter to eliminate abstractions as it is for it to gather up scattered facts and theories to unite them into an integral system. Although elements of abstraction still remain, they are reduced to a minimum by the increasing tendency to demand not only an algebraic symbol, but a visual picture of the processes of nature.

## II

It is perhaps not surprising that the astonishing progress of general physics during recent times should thus far have failed to exert any very notable influence upon the science of biology. From the point of view of the *physicist*, *biological problems must be regarded as questions of special material structure*, usually of a very intricate character, and involving the arrangement and history of units of matter for the most part larger than those upon which his attention is immediately concentrated. The program of modern physics is to build up the theory of all material structures by means of geometry and the dynamics of electrical particles. The first problem, logically, is that of the constitution of the atom, and as the solution of this problem is still unfinished, too much should not be expected of our knowledge of the configuration of particles and forces in higher aggregates of matter.

However, a critic who sees current events in the light of the history of science can hardly escape a twinge of disappointment at the recrudescence in biological theory, at the present time, of the doctrine of *vitalism*. The present, of all periods in the history of thought, is an hour of triumph of the monistic theory of nature, and yet now,

more frequently than during the nineteenth century, men eminent in biology seem to quail before the complexity and delicacy of the life process, and, while uttering mechanistic truths about life, to offer them as sacrifices to a spirit of vagueness and discouragement.<sup>3</sup>

It is my belief that this rejuvenation of mysticism and Aristotelian teleology is due not so much to a natural admiration on the part of biologists for obscure ways of thinking, as to their neglect of modern physics and of the methods of thought pursued in that science. It is the purpose of this paper, which is intentionally polemical in manner, to rebuke this tendency by commending to the attention of biologists a general speculation concerning the life process, which—although incapable of immediate verification in all of its aspects—does answer the most perplexing questions raised by vitalism, and at the same time forms a perfectly distinct bond between biological theory and the modern theory of matter.

It is not improbable that the future will look back upon contemporary theoretical biology as a reactionary phase in the history of the science. The great synthetic energy of the Darwinian theory has been spent, has accomplished its magnificent results, but has left many tattered ends, by means of which a few of its enemies are attempting to tear down the entire structure once more. Even the remarkable discoveries which are classed under the name Mendelism are sometimes turned against the mechanistic conception of evolution. These discoveries, although patently of fundamental importance for the theory of life-processes, have as yet provided us with no new synthetic instruments of thought, but instead have generated an amazing and ever-growing list of abstract concepts. However, these concepts do furnish us with a means for the analysis of species in terms of their genetic determination and the recent studies of Morgan<sup>4</sup> and Goldschmidt<sup>5</sup> in

<sup>3</sup> Consider, for example, the contents of Haldane's recent address on "The New Physiology," *Science* (1916), N. S., 44, 620-632.

<sup>4</sup> Morgan, T. H., and others, "The Mechanism of Mendelian Heredity," 1915.

<sup>5</sup> See Goldschmidt, R., "Genetic Factors and Enzyme Reaction," *Science*

this field are pointing the way to synthetic considerations of far-reaching significance.

That biologists recognize the need of new light in the theory of heredity and of evolution, is clearly shown by the following quotations, from Bateson's Silliman lectures:

In spite . . . of the general attention devoted to the study of variation and the accumulation of material bearing on the problem, no satisfactory or searching classification of the phenomena is possible. The reason for this failure is that a real classification must presuppose knowledge of the chemistry and physics of living things which at present is quite beyond our reach. It is however becoming probable that if more knowledge of the chemical and physical structure of organisms is to be attained, the clue will be found through genetics, and thus that even in the uncoordinated accumulation of facts of variation we are providing the means of analysis applicable not only to them, but to the problems of normality also.

Again:

Somewhat as the philosophers of the seventeenth and eighteenth centuries were awaiting both a chemical and a mechanical discovery which should serve as a key to the problems of unorganized matter, so have biologists been awaiting two several clues. In Mendelian analysis we have now, it is true, something comparable with the clue of chemistry, but there is still little prospect of penetrating the obscurity which envelops the mechanical aspect of our phenomena.

Again:

When with the thoughts suggested in the last chapter we contemplate the problem of evolution at large, the hope at the present time of constructing even a mental picture of that process grows weak almost to the point of vanishing. We are left wondering that so lately men in general, whether scientific or lay, were so easily satisfied. Our satisfaction, as we now see, was chiefly founded on ignorance.<sup>6</sup>

It will be perceived that the demand made by Bateson in these passages is not for new biological facts, but for physico-chemical conceptions in terms of which a chaos of biological facts, already at hand, can be explained, or systematized. Moreover, the emphasis is laid entirely upon the inability of the mind to conceive an explanation,

(1916), 43, 98-100. Also "Experimental Intersexuality and the Sex Problem," *AMERICAN NATURALIST* (1916), 50, 705-719.

<sup>6</sup> Bateson, W., "Problems of Genetics" (1913), 31, 32, and 97.

or a synthesis of these facts, rather than upon the necessity of detailed proof of some explanation which has already been offered. The contents of genetics would verify the proper conceptions if the human mind were only capable of suggesting them.

In another place,<sup>7</sup> Bateson says, with reference to the mechanism of cell division:

It is, I fear, a problem rather for the physicist than for the biologist. The sentiment may not be a popular one to utter before an assembly of biologists, but looking at the truth impersonally, I suspect that when at length minds of first rate analytical power are attracted to biological problems, some advance will be made of the kind which we are awaiting.

As a matter of fact, in the school of the physical chemists there has been in preparation, since the days of Thomas Graham, a system of knowledge which, even in its present unfinished form, has a most important and direct bearing upon mooted biological problems. This is the science of the *colloidal state*. The difficult abstractions and elaborate classificatory scheme, in terms of which the theory is now stated, will tend to be cleared up as our study of colloids comes definitely under the dominion of the general electro-molecular theory of matter. Intimate contact with the latter has already been established, indeed, through recent remarkable contributions by Langmuir,<sup>8</sup> dealing with the atomic constitution of solids and liquids. It is to colloidal chemistry that we must look for answers to the large majority of the fundamental problems of vital activity. These answers will be slow in appearing, however, if we refuse to look.

In fairness, it must of course be admitted that many biologists are keenly alive to the importance of the theory of matter, and especially of the theory of colloids, for the advancement of their science. However, possibly because the majority of these men are specialists in biochemistry, there seems to be a lack of coherent applications of mod-

<sup>7</sup> *Loc. cit.*, 41.

<sup>8</sup> Langmuir, I., "The Constitution and Fundamental Properties of Solids and Liquids," *Journal of the American Chemical Society* (1916), 38, 2221-2295; and other forthcoming papers in the same journal and in the *Physical Review*.

ern physico-chemical ideas to the problems of evolution and heredity, which make up the heart of the biological mystery.

It has for some years been my conviction that the conception of *enzyme action*, or of *specific catalysis*, provides a definite, general solution for all of the fundamental biological enigmas: the mysteries of the origin of living matter, of the source of variations, of the mechanism of heredity and ontogeny, and of general organic regulation.<sup>9</sup> In this conception I believe we can find a single, synthetic answer to many, if not all, of the broad, outstanding problems of theoretical biology. It is an answer, moreover, which links these great biological phenomena directly with molecular physics, and perfects the unity not alone of biology, but of the whole system of physical science, by suggesting that what we call life is fundamentally a product of catalytic laws acting in colloidal systems of matter throughout the long periods of geologic time. This view implies no absurd attempt to reduce every element of vital activity to enzyme action, but it does involve a reference of all such activity to some enzyme action, however distantly removed from present activity in time or space, as a necessary first cause. Catalysis is essentially a determinative relationship, and the *enzyme theory of life*, as a general biological hypothesis, would claim that all intra-vital or "hereditary" determination is, in the last analysis, catalytic.

The conception of enzyme action is, of course, one with which all biologists, including students of genetics, are extremely familiar.<sup>10</sup> Probably there is no student of morphogenesis who would not consider it absurd to deny that enzymes play a very important rôle in individual development. In a number of cases such participation has been clearly demonstrated by experiment, and the suggestion that the germ-cell contains "determiners" for

<sup>9</sup> See my two papers: "The Chemical Origin and Regulation of Life," *Monist* (1914), 22, 92-134; and "The Enzyme Theory of Life," *Cleveland Medical Journal* (1916), 15, 377 ff.

<sup>10</sup> On enzyme action in general, see Bayliss, W., "The Nature of Enzyme Action," 1914.



the production of enzymes, which, in turn, regulate certain aspects of the development, is a common one.<sup>11</sup> Several Mendelians have even hinted that the "unit characters" themselves are enzymes,<sup>12</sup> but so far as I am aware, no worker in genetics, with the exception of Goldschmidt, has regarded this conception as an important one.<sup>13</sup> Indeed, in the face of the nearly self-evident, they have turned away to vitalism and despair.

Consider, for example, the following quotation from Bateson.

We must not lose sight of the fact that though the factors operate by the production of enzymes, of bodies on which these enzymes can act, and of intermediary substances necessary to complete the enzyme action, yet these bodies themselves can scarcely be genetic factors, but consequences of their existence. What are the factors themselves? Whence do they come? How do they become integral parts of the organism? Whence, for example, came the power which is present in a White Leghorn of destroying—probably reducing—the pigment in its feathers?<sup>14</sup>

It is my contention in this and previous papers that statements of this sort can hardly represent anything less than intellectual blindness. On the supposition that the actual Mendelian factors are enzymes, nearly all of these general difficulties instantly vanish, and I am not acquainted with any evidence which is inconsistent with this supposition.

### III

Up to very recent times, although a great number of hypotheses to explain catalysis were in existence,<sup>15</sup> no

<sup>11</sup> See, for example, the following: Loeb, J., and Chamberlain, M. M., "An Attempt at a Physico-Chemical Explanation of Certain Groups of Fluctuating Variations," *Journal of Experimental Zoology* (1915), 19, 559-568. Moore, A. R., "On Mendelian Dominance," *Archiv für Entwicklungsmechanik* (1912), 34, 168-175. Riddle, O., "Our Knowledge of Melanin Color Formation and its Bearing on the Mendelian Description of Heredity," *Biological Bulletin* (1908), 16, 316 ff.

<sup>12</sup> See Bateson, "Mendel's Principles of Heredity," 1909, 268.

<sup>13</sup> The speedy publication of experimental results of great importance in this connection is promised by Goldschmidt. See above references.

<sup>14</sup> Bateson, "Problems of Genetics," 86.

<sup>15</sup> A comprehensive review of these theories and of the facts of catalysis and fermentation is given by Mellor, J. W., "Chemical Statics and Dynamics," 1914, 245-383.

completely satisfactory general theory of the process could be formulated. In this state of affairs, the use of the conception as a general explanatory agent in biology, could not be said to establish an unequivocal bond between biological regulation and the theory of matter. At the present day, however, it is possible to frame a hypothesis to account for catalytic action, which has general applicability and at the same time rests directly upon the ideas of modern molecular physics.

Ostwald defines a catalytic agent as "a substance which changes the velocity of a reaction without itself being changed by the process."<sup>16</sup> In the older terminology of the pioneer, Berzelius, it is "a substance which, merely by its presence and not through its affinity, has the power to render active affinities which are latent at ordinary temperatures."<sup>17</sup> According to Ostwald, catalytic power is a universal property of matter, for he says:

There is probably no kind of chemical reaction which cannot be influenced catalytically, and there is no substance, element, or compound which can not act as a catalyzer.<sup>18</sup>

This being the case, it should often occur that a substance will catalyze a reaction which generates further quantities of the same substance, a process known as *autocatalysis*. Catalytic relationships may thus be classified into the autocatalytic and the *heterocatalytic*. I shall attempt to show that the former may be the more fundamental of the two relationships, and that reasons can be adduced for regarding autocatalytic power as a necessary property of every complex form of matter.

Perhaps the simplest illustration of a catalytic effect of any sort is that of the production of crystallization in a supersaturated solution of some substance by the introduction of a small crystal of the same substance. This of course has the form of an *autocatalytic* process. Although effects of this kind are included in Ostwald's classification of varieties of catalysis,<sup>19</sup> up to recent times

<sup>16</sup> Mellor, *loc. cit.*, 250.

<sup>17</sup> *Ibid.*, 246.

<sup>18</sup> *Ibid.*, 254.

<sup>19</sup> *Ibid.*, 255.

it might have been possible to raise a legitimate objection to the illustration on the ground that the induced change is not a chemical one. However, this objection is definitely disposed of by the recent work of the Braggs, and others, on the constitution of crystals,<sup>20</sup> which has shown that the unit of structure in solid bodies is usually the single atom, and not the molecule, since in crystals there is, as a rule, no exclusive arrangement of the atoms into molecular groups. The spacing of the atoms is such as to make it clear, moreover, that the forces which hold the total crystal system together are identical with those which we regard as underlying chemical affinity. In other words, in the crystal there is either no distinction between inter-atomic and inter-molecular forces (*i. e.*, between chemical affinity and cohesion), or else the entire crystal must be considered to be a huge polymeric molecule.<sup>21</sup> It is therefore perfectly legitimate to treat the process of crystallization as a chemical change, and to regard the initiation of this process under the conditions above described, as an example of autocatalysis, which may well be typical.

Although the results of crystal analysis indicate that no distinct molecules are to be found in the solid state, this is not true of the dissolved, or of the gaseous state. Moreover, on account of the fact that their component particles are held in place by forces of electrical attraction and repulsion, all molecules must possess their own fields of electrical force, and the field of any molecule must have a spatial form which is characteristic of that molecule. These field patterns will thus be different in the molecules of substances which differ chemically, and will be similar in molecules of the same or of an allied chemical substance.<sup>22</sup> The forces of cohesion in a crystal may be thought of as resulting from the fusion of a large number of these molecular fields into a continuous mosaic, and in such manner that their several axes are parallel.

<sup>20</sup> See Bragg, W. H., and W. L., "X-Rays and Crystal Structure," 1915.

<sup>21</sup> Cf. Langmuir, *loc. cit.*, 2221-2222.

<sup>22</sup> See Comstock and Troland, *loc. cit.*, 86-89.

However, such fusion can not fail to have an influence upon both the form and the strength of the fields in question, since it involves a redistribution of the atomic forces. This will take the form of an opening out, or expansion, which will necessarily reduce the coherence of the group of atoms originally forming the individual molecule. The degree of this "opening" of the field which occurs in crystallization must vary with the nature of the molecule, and is probably smaller for organic substances than it is for the majority of inorganic compounds.

The mechanism of the autocatalytic process of crystallization may be described somewhat as follows:

In a solution, or a gas, the molecules of the dissolved substance move about at random among the molecules of the solvent, and the orientation of the axes of their fields is entirely haphazard. However, as soon as a crystal of the solute is introduced, the field forces of the surface layer of atoms attract the dissolved molecules and at the same time tend to turn them on their axes so that, as they condense, they will fall into the pattern of the "space lattice" upon the plan of which the crystal is built.<sup>23</sup> As this is the most stable position which they can assume, they will tend to remain there and form a new surface layer of the crystal, to act in turn upon further molecules in the solution, until all of the surplus dissolved substance has been deposited.

The primary force bringing the molecules to the crystal face is of course not the surface field of attraction—surface tension field—but their temperature motion—or osmotic pressure. A similar force, of lower magnitude in the case of a supersaturated solution, is constantly disengaging molecules from the crystal and throwing them back into the solution. The action apparently ceases when the number of molecules deposited upon the crystal surface in unit time becomes reduced—owing to decreasing concentration—to an equality with the number leaving in the same interval.

<sup>23</sup> Cf. *ibid.*, 113.

The essential feature of the above described mechanism for the autocatalytic production of polymeric molecules may be illustrated to the eye by means of a model consisting of a board with a large number of small compass needles mounted upon it. If these needles are freed from the action of the terrestrial magnetic field and are then shaken into a random orientation, they may remain in this condition indefinitely. However, if a small number of adjacent needles be turned by some outside force so as to acquire a common direction, their combined magnetic fields will cause other neighboring needles to swing into line, so that the action must spread to all of the needles on the board. The field of an ideal compass needle has a simple bipolar pattern, and a symmetrical distribution of forces. In the cases of specific atoms and molecules, however, this is probably seldom true. Nevertheless, the general principles involved in their dynamic interaction would remain the same as those for the case of the compass needles.

It is clear that the explanation of autocatalysis above given accounts immediately only for the synthesis of polymeric molecules from individual units which are all alike. As a rule, chemical changes involve the interaction of different units, and it can easily be seen that the same general mechanism will apply to the catalysis of reactions of this sort as to that of simple crystallization. The principles involved in the process have been made especially clear in the recent articles of Langmuir.<sup>24</sup> Consider first a solution containing two kinds of molecules which can be deposited upon a crystal surface consisting of an orderly arrangement of these two molecular groupings in mosaic or lattice form. The second species of molecules may be considered, for example, to be those of the solvent, as in the case of "water of crystallization." There will be certain "elementary spaces"—as Langmuir calls them—upon the surface of the crystal, which will especially attract and orient the water molecules, and adjacent elementary spaces which will act in the same way upon the

<sup>24</sup> *Loc. cit.*, 2286-2292.

molecules of the solute. In this way the crystal or polymeric molecule will be built up out of two components by the simultaneous and parallel action of two initially combined species of molecular fields. This change is catalyzed by the crystal, and is an autocatalytic process involving the synthesis of two substances. It is clear that any number of substances may be influenced in this way by a similar, but more complex initial crystal form.

However, our explanation still remains somewhat special in its application, as in the majority of cases the products of catalysis do not adhere permanently to the catalytic surface. The extension of the explanation to cases of this sort is not difficult, since we have already seen that, even in the case of crystallization, the heat vibrations of the atoms are constantly throwing off molecular groups from the surface of the solid. As pointed out by Langmuir, the attraction between the surface and two molecular groups which have a strong affinity for each other may be less than the sum of the attractions of the surface for each of the groups, when separate.<sup>25</sup> This is due to the "closing up" or contraction of the fields of force of the groups as they come together. Hence combined groups of this sort will be more easily detached from the surface than will the uncombined groups, which will tend to be held in place until their mates fall into the right positions. The catalytic surface thus acts like an orienting sieve which on account of its special structure forces a chaotic crowd of individuals which come into contact with it, to fall into a special configuration. Many machines which accomplish exactly this effect are in use in the industries.

Thus far we have dealt only with the mechanism of autocatalysis. Heterocatalysis is probably to be regarded as an extension of the process of autocatalysis. It is obvious that exact similarity of the force patterns of the catalyzing and catalyzed systems is not essential. Indeed, the catalytic effect which is based upon direct similarity of structure between the two systems should be

<sup>25</sup> *Ibid.*, 2257, 2264-2266.

much weaker than that which accompanies certain types of structural *correspondence*, such as that existing between a body and its mirror-image, or between a lock and a key. Special structural relations of this sort probably exist between stereochemical isomers, between acids and bases, etc. It is easily conceivable that the patterns of certain surfaces may be capable of distorting other special configurations which come under their influence, so that they fall into new equilibrium figures, without these figures being of necessity identical with those of the catalytic system. The general principles of the action, however, remain the same.

Catalytic synthesis is a less common process in the laboratory than is destructive catalysis, but the laws of energy necessitate both effects, if either one is possible. Consequently the mechanism which we have described above must be an exactly reversible one, and must assist in the decomposition of molecular complexes as much as it aids in their synthesis. The deposition of the molecules to be decomposed, upon the catalytic surface would naturally follow the same principles as those stated for simple polymerization. In this state of deposition the field forces of the crystal surface would inevitably have a tendency to open up the field of the deposited molecule, thus rendering it more unstable than before, in which condition the temperature vibrations of the system could break it up more easily than in the undeposited state.

This weakening of the internal bonds of the molecule in the field of the catalytic surface corresponds with the weakening of forces of electrical attraction by increasing the "dielectric capacity" of the medium in which an electrical system is contained. It is the same action which permits water to dissociate neutral molecules into ions,<sup>26</sup> and is probably responsible for the high catalytic power of water, in general. However, in detail, the process must be a "personal" affair between individual water molecules and molecules of the dissolved substance, just as in the case of the crystal surface, since the ionizing effect

<sup>26</sup> Cf. Comstock and Troland, *loc. cit.*, 139-140.

of water does not appear to depend merely upon the chemical instability of the solute.

The increase in reaction velocity which characterizes catalysis is to be attributed to three more or less separable influences exerted by the catalytic surface, (1) the local increase in the concentrations of the reacting substances at the surface, (2) the impressment upon the attached molecules, of a relative orientation which is favorable to chemical union, or which in part constitutes such union, and (3) the spreading and weakening of the fields of force of the molecules, due to their interaction with the surface fields. The first factor, alone, would be of primary importance for the combination of free atoms—a relatively rare process—while the last factor, alone, would be responsible for the acceleration of simple decompositions. Reactions between two or more molecular *groups*, whether synthetic or metathetic, should be influenced by all three factors. Strutt<sup>27</sup> has shown that in certain typical chemical reactions, only one out of many millions of collisions between potentially reactable molecules results in chemical interaction. The active collisions probably coincide with the presence in the colliding system of favorable relative orientations and states of the molecular fields, which in the absence of a catalyzer depend upon chance, but which in the presence of a catalyzer are encouraged by the nature of the catalytic surface.

It is of course not possible in a paper of this sort to enter into the mathematics of the theory of catalysis which is outlined above.<sup>29</sup> Catalytic influence is obviously only one among many factors which affect a chemical reaction. Catalysis is possible only when the appropriate raw materials are provided, and when the energy relations of the system are such as to make the reaction thermodynamically conceivable. The heterocatalytic effect of a given substance may far outweigh its autocatalytic effect either

<sup>27</sup> Strutt, R. J., "Molecular Statistics of Some Chemical Actions," *Proceedings of the Royal Society* (1912), A, 87, 302-309.

<sup>28</sup> Cf. Mellor, *loc cit.*, 250-254. Also Bayliss, *loc. cit.*, 49-71.

<sup>29</sup> For a development of the mass action relationships involved, see Langmuir, *loc. cit.*, 2287 ff.



because the energy changes do not favor the latter, or because in a given system the raw material for the autocatalytic reaction is absent, while that for the heterocatalytic reaction is present in abundance.

However, the above considerations would lead us to believe that all substances should show some tendency to form polymeric molecules or crystals. This appears to conflict with the classical division of substances into crystalloids and colloids, but this division, like all others, can not be expected to stand unmodified by the modern analysis. There is plenty of evidence from direct observation that many colloidal particles are simply very small crystals.<sup>30</sup> On the other hand, the molecules of polymeric substances of high molecular weight, such as starch and certain proteins, are probably of the same order of magnitude as small colloidal particles. From the point of view of the theory of matter, there is no fundamental difference between the general plan of a starch molecule and that of a crystal of sugar, and it is highly probable that the distinction between colloids and crystalloids rests upon purely quantitative relations, respecting the size of the polymeric structures (crystals) produced under ordinary conditions.

Large crystals are formed easily by simple substances whose molecules have open fields of force or highly unsaturated attractions. Small crystals are characteristic of more complex substances, common among the compounds of carbon, having relatively closed fields. Large mosaics of such molecules become unwieldy and are easily disrupted by the temperature vibrations. They are also built up more slowly than are mosaics of molecules with open fields. The distinction between these two classes of molecules is of course merely quantitative; no type of molecule has a completely closed field, and on the other hand no substance is capable of forming indefinitely large crystals in a finite length of time. The atomic structure of the solid phase of a colloidal gel is probably analogous

<sup>30</sup> See Ostwald, Wo., "A Handbook of Colloid-Chemistry," English translation, 1915, 56-66.

to that of the mass of small crystals, compacted together, which always results from the rapid crystallization of a supersaturated solution of a substance like, *e. g.*, sodium thiosulphate.

It is evident, then, that the general theory of catalysis which has been outlined is applicable to *enzyme action*, which almost certainly depends upon the deposition, or *adsorption* of the reacting substances upon the surfaces of colloidal particles.<sup>31</sup> Such adsorption, the molecular mechanism of which has been made very clear by Langmuir,<sup>32</sup> will tend to be specific, and the more specific the more complex is the structure of the units making up the mosaic of the surface. Molecules the field patterns of which fit closely into the fields of the surface will tend to displace others having a cruder correspondence. This follows from either electro-dynamics or thermodynamics, and obviously coincides with Fischer's classical conception of the lock and key relation between enzyme and substrate.<sup>33</sup>

It will be perceived that our theory of the catalytic process is simply a refinement and extension of the classical theory of "intermediate compounds," which has been proven true in so many instances.<sup>34</sup> "Adsorption compounds," which play the principal rôle in enzyme action, do not differ dynamically from chemical compounds in general, since the forces causing adsorption are the same as those responsible for chemical union. Conversely, catalytic action in which the catalyst is in a molecular or unpolymerized state will not necessarily differ in its mechanism from that characteristic of enzymes or of metallic surfaces.

#### IV

The suggestion that the fundamental life-process of *growth* is the expression of an autocatalytic chemical re-

<sup>31</sup> See Bayliss, *loc. cit.*, 104-123.

<sup>32</sup> *Loc. cit.*, 2267-2278.

<sup>33</sup> See Mellor, *loc. cit.*, 363.

<sup>34</sup> Cf., *e. g.*, Kendall, J., and Booge, J. E., "Studies on Catalysis. I. The Addition Compounds of Esters with Organic Acids," *Journal of the American Chemical Society* (1916), 38, 1712-1736.

action has been made independently by a number of investigators.<sup>35</sup> It will be perceived that on the basis of the foregoing theory of autocatalysis, this suggestion becomes closely allied to the familiar and ancient comparison of vital growth to the growth of a crystal. The customary objection to this comparison, viz., that a crystal grows by accretion whereas protoplasm increases by intussusception, loses its force as soon as we regard living matter as a complex mixture of substances suspended by colloidal subdivision in water, since there is no evidence that the individual colloidal particles do not grow by accretion. On the contrary, it is almost inconceivable that these bodies, which are the real chemical units of protoplasm, should grow in any other way. The growth of a system like a cell could be regarded as the resultant effect of a very large number of component growths, each governed by its specific autocatalytic mechanism. It has been shown by T. B. Robertson<sup>36</sup> that growth curves, with respect to the time, actually do coincide in general form with the curve characteristic of an autocatalytic reaction.

A multitude of observations substantiate the belief that the internal determination of cell-life rests primarily with the nucleus,<sup>37</sup> or with the chromatin substance of the cell, when no well-defined nucleus is present. Even in the highly organized cell, this substance can be seen to possess a mosaic structure, and it can be shown that for a given species this structure is sensibly constant,<sup>38</sup> so that it is necessary to suppose that a reduplication of chromatin units occurs with each cell-division. This process of reduplication is apparently made visible to us in mitosis.

<sup>35</sup> See, for example, Ostwald, W., "Ueber die zeitlichen Eigenschaften der Entwicklungsvorgänge." *Vorträge und Aufsätze über Entwicklungsmechanik des Organismus*, herausgegeben von W. Roux (1908), Heft 5, Leipzig.

<sup>36</sup> Robertson, T. B., "On the Normal Rate of Growth of an Individual and its Biochemical Significance," *Archiv für Entwicklungsmechanik* (1908), 25, 581-615; and subsequent articles in the same journal.

<sup>37</sup> See Wilson, E. B., "The Cell in Development and Inheritance," second edition, revised (1911), 30-31, 341-354.

<sup>38</sup> Cf. Boveri's *Individualitäts Hypothese* and "law of proportional nuclear growth."

The simplest hypothesis to account for such reproduction lies in the supposition that each unit can give rise to another unit substantially identical with itself.

The Weismannian theory of the constitution of the germ plasm,<sup>39</sup> which is typical of the so-called "corpuscular theories" of the life-process or of heredity, also demands the existence of vital elements, each possessing the power of reproduction *ad infinitum*. The general conceptions of this theory appear to find verification, first, in the facts already mentioned, and second, in the discoveries of Mendelism. The recent work of Morgan and his collaborators,<sup>40</sup> moreover, reveals clearly the intimate connection which exists between the corpuscular "unit characters" of Mendelian heredity and the histological units present in the chromosomes. Consequently, it would seem to be a fairly safe generalization, or at least an extremely probable hypothesis, which states that the distinctive properties of cells, tissues, and species are primarily determined by the nature of systems of colloidal particles contained in cell-nuclei and, originally, in some germ-cell nucleus.

However, in spite of the seeming strength of the evidence, some biologists are of the opinion that such a view as this must be rejected because it paralyzes thought. Consider, for example, the following quotation from Child.<sup>41</sup>

It is scarcely necessary to call attention to the fact that these [corpuscular] theories do not help us in any way to solve any of the fundamental problems of biology; they merely serve to place these problems beyond the reach of scientific investigation. The hypothetical units are themselves organisms with all the essential characteristics of the organisms that we know; they possess a definite constitution, they grow at the expense of nutritive material, they reproduce their kind. In other words, the problems of development, growth, reproduction, and inheritance exist for each of them, and the assumption of their existence brings us not a step nearer the solution of any of these problems. These theories are nothing more nor less than translations of the phenomena of life as we know them into terms of the activity of

<sup>39</sup> Weismann, A., "The Germ Plasm," English translation, 1893.

<sup>40</sup> *Loc. cit.*

<sup>41</sup> Child, C. M., "Senescence and Rejuvenescence," 1915, 11-12.

multitudes of invisible hypothetical organisms, and therefore contribute nothing in the way of real advance. No valid evidence for the existence of these units exists, but if their existence were to be demonstrated we might well despair of gaining any actual knowledge of life.

We have in this passage a clear statement of the essentiality of growth, as self-reduplication of specific substance, in the life-process. Consideration of Child's remarks will show that the difficulties which he raises are almost completely dissolved as soon as we postulate for the biological corpuscles the power of autocatalysis. In the light of our previous discussion, it can not be claimed that this is purely a verbal solution of the problem, as we have advanced definite reasons for believing that autocatalytic activity is a property of all chemical substances whatsoever, given the appropriate chemical environment. Since the environment of the chromatin particles has been made to order by evolution, the force of Child's criticisms would seem to be nil. Moreover, he certainly underestimates the importance of the facts which point to an actual corpuscular determination of vital functions.

In view of this, it would appear advisable to accept the *Elementarorganismen*<sup>42</sup> as if they were clearly established facts, and proceed to consider what further light can be thrown upon biological problems by the conception of specific catalysis.

It is well known that in many cases, at least, the nucleus controls cell activity by liberating enzymes,<sup>43</sup> and the mass activity of cells in the form of specific tissues has been satisfactorily proven to depend, so far as it is directly chemical, upon the presence in these tissues of specific enzymes. In the field of general adult metabolism the determinative importance of catalysis would appear to be no longer a matter of debate. Analogy would lead us to believe that the same principle is of prime importance in the metabolism of development.

In laying emphasis upon the cardinal importance of the

<sup>42</sup> See Brücke, *Sitzungsbericht, Akademie der Wissenschaften, Wien*, (1861), 44, (2), 381-406.

<sup>43</sup> See Mann, G., "The Chemistry of the Proteids," 1906, 454 ff. Also, Loeb, J., "The Dynamics of Living Matter," 1906, 7-29.

enzyme for organic regulation we must of course recognize that the exact effects produced by catalysis depend, at all stages of development, upon the manner of its co-operation with other physical principles, which may involve the functioning of molar structures already present. However, as we retrace the course of ontogeny and of the evolution of any specific germ-cell, we should find that the number and importance of such structures decrease, although the construction of any given tissue-form always depends upon the action of specific enzymes in conjunction with preëxisting tissue structures. It is not to be doubted for an instant that important preëstablished structures exist even in germ-cells, and enter into the determination of their activity. It is therefore unfair to demand a catalytic explanation of such a complex process as karyokinesis, which shall not take into consideration the history or evolution of the cell.

The task of elucidating the exact mechanism by means of which vital regulation is maintained, and especially of showing how, in accordance with recognized principles of physics, a complex of specific, autocatalytic, colloidal particles in the germ-cell can engineer the construction of a vertebrate organism, is truly so formidable that it is unkind for the vitalist arbitrarily to deny us the use of any of these recognized principles. For example, we must be permitted to suppose that a large number of variables can unite in the production of a single effect. The greater part of the modern vitalistic worry over "organization" and vital "equilibrium"<sup>44</sup> appears to depend upon a tacit assumption, either that physical laws are not reliable, or that it is impossible for a number of variables to control simultaneously a single process. Both of these assumptions are self-evidently counter to the most fundamental presuppositions of physical analysis.

Although the fundamental life-property of the chromatin units is that of autocatalysis, it is necessary and legitimate to suppose that the majority of them sustain specific heterocatalytic relationships to reactions oc-

<sup>44</sup> Consider, for example, Haldane, *loc. cit.*

curring in living matter. This is because nuclear material makes up a relatively small percentage of protoplasm, and because the reactions governed by enzymes are ordinarily heterocatalytic.

It is a remarkable fact that the chemistry of the cell-nucleus has reached a stage of advancement superior to that attained by the chemistry of the cytoplasm. It appears that the essential constituent of chromatin is a substance called nuclein, which is composed of a basic, protein factor and nucleic acid. The facts indicate that the acid factor is the permanent and essential component of the nucleus, and organic chemical analysis seems to prove that only one kind of nucleic acid exists in animal tissues, although a different variety is to be found in the cells of plants.<sup>45</sup> If, as now seems probable, the genetic enzymes must be identified with the nucleic acids, we shall be forced to suppose that these substances, although homogeneous—in animal or plant—from the point of view of ordinary chemical analysis, are actually built up in the living chromatin, into highly differentiated colloidal, and colloidal-molar, structures. The apparent homogeneity results from the fact that ordinary chemical analysis provides us only with the *statistics of the fundamental radicles* which are involved.

To some minds, the idea that a portion of matter as small as a germ-cell can contain sufficient catalytic substance to control the destinies of a complex organism, seems hardly plausible. However, considering the slowness of such processes as growth, it is clear that the quantity of catalyzer required will usually be smaller than that used in laboratory experiments; and it is a truism in chemistry that radical alterations of reaction velocities can be caused by the presence of almost infinitesimal amounts of catalytic material.<sup>46</sup> From the nature of the process, it is evident that only a *few molecules* of substance will be required to furnish the basis for an *auto-catalytic* reaction which may eventually result in the pro-

<sup>45</sup> See Jones, W., "The Nucleic Acids," 1914.

<sup>46</sup> See Mellor, *loc. cit.*, 248-249.

duction of any desired amount of this substance; and a simple calculation shows that the chromatin of the human zygote has sufficient volume to contain about one quadrillion ( $10^{15}$ ) molecules the size of that of oxygen.<sup>47</sup>

In order that the enzymes of the germ-cell should be able to determine the form of the mature organism, they must have the power to govern (1) the physical and chemical properties of specific tissue material, (2) the position of specific tissues, (3) the size of these tissues and (4) their form. Since the physical properties of any piece of matter depend upon its chemical constitution, and since any chemical change can be regulated by catalysis, the mere presence of a specific catalyzer in a favorable mixture is sufficient to determine the production of matter of any possible variety, in any possible amount. It is always necessary to assume that the history of an organic system is such as to have provided it with the raw materials necessary to its activities. If this is not the case, the system naturally perishes of "starvation."

The most primitive form of cell-division involves nothing more than reduplication, and this is the law of multiplication of the germ-plasm. Driesch<sup>48</sup> argues that to explain the reproduction of a nuclear "machine" which determines development, we must postulate another machine to carry out the operation, and so on *ad infinitum*. The nature of the autocatalytic process, however, shows that this conclusion is in error, since pure autocatalysis would tend to bring about an exact qualitative reproduction of any given plane or linear mosaic of specific units. In a nutritive medium such a mosaic would tend to grow in all of its parts by the deposition of similar substance. Primitive nuclear division (as, *e. g.*, in the Protista) may depend solely upon the physical instability of colloidal particles greater than a certain size, but it can hardly be

<sup>47</sup> This calculation is based on the following assumptions: (1) that the diameter of the germ-cell nucleus is .05 mm., and (2) that the molecules fill only one-sixth of the total volume of the nucleus.

<sup>48</sup> Driesch, H., "The Science and Philosophy of the Organism," 1908, 2, 341.



doubted that the complex mechanism of mitosis rests upon definite structural machinery, established by long periods of evolution.

In order to account for the differentiation of cell-nature which occurs in ontogeny, Weismann was led to assume a thoroughgoing differential segregation of the biophores of the original germ-cell in the course of embryological development; in other words, he supposed that in this process the rule of nuclear division is differentiation and not reduplication. This assumption, although undoubtedly a partial truth, is neither necessary nor in harmony with general biological probabilities, in the form in which it was made by Weismann.<sup>49</sup> Consequently the difficulties into which it has led his general theory, can be regarded as without important bearing upon the acceptability of corpuscular hypotheses at large.

Since reduplicating division is the established rule among unicellular organisms—which must have had a long evolutionary history—we should expect this rule to be conserved as far as possible in multicellular evolution. According to the general law of recapitulation, this should be especially true for the primary stages of ontogeny, for which Driesch's principle of the "equipotential system" appears often to hold. The blastula may well be simply an undifferentiated mass of germ-cells, analogous to a homogeneous colony of unicellular forms. Rudimentary differentiation may be brought about and determined by specific enzyme constitution, without differential partitionment of enzymes in segmentation, since the forces acting upon any cell must depend upon its *position* in the mass, and the activation or inhibition of a given enzyme may be conditioned by the presence of definite stimuli in definite intensities. This being the case, any cell could assume germinal characters if isolated from the total mass.<sup>50</sup>

<sup>49</sup> Weismann's theory, it must be recognized, assumes "doubling division" for the early stages of segmentation, a law which continues to hold for the "germ-tracks."

<sup>50</sup> Cf. Hertwig, O., "Evolution or Epigenesis," English translation, 1896.

However, the facts of "crossing over" observed in recent studies on the relation between Mendelian characters and chromosome constitution<sup>51</sup> show that the latter is not inviolate, even in purely germinal segmentation. Since the power possessed by cells to assume germinal character, even to the limited degree of being able to regenerate a single organ or tissue, seems to vary in inverse proportion to the degree of specialization of the cells, it is reasonable to suppose that Weismann's principle of differentiating division actually does operate in the higher stages of development. However, at no stage is it the only mechanism of differentiation, and it certainly is not the primitive means.

It is possible that cancer represents a return of tissue cells to a germinal or semi-germinal stage, due to the failure of a "stimulus of differentiation" to remain effective.

The control by the *genetic enzymes* of the position, size and form of specific tissues must involve, first, a quantitative regulation of the process of differentiation, which can be effected by the establishment of definite relations between the chemical constants of the catalytic reactions and the conditions under which the course of development necessarily places them; and, second, control of the planes of segmentation of the cells. To attempt a specification of the exact process by which this latter factor can be governed by the chemical constitution of the cell-nucleus, lies beyond the scope of the present paper, but it should be pointed out that in the last analysis chemical constitution means nothing but a definite spatial arrangement of electrical forces, so that there is nothing paradoxical in the determination of "pure form" by chemical agents.

As is evident in the quotations made above from Bateson, the dominant problem in the modern discussion of evolution is that of *the origin of variations*. It is the failure of Neo-Darwinians to explain the appearance of variations, and especially of new unit characters, which has led such writers as Driesch, Korschinsky and Wolff

<sup>51</sup> See Morgan, *loc. cit.*,

to speak of the "episode of Darwinism" and of *Das Sterbelager des Darwinismus*.<sup>52</sup> The enzyme theory of vital determination brings new life to the doctrine of evolution by accidental variation and natural selection, first, by showing that all fundamental variations should be discontinuous, or heterogenetic, as demanded by the mutation theory of De Vries, and second by revealing the exact mechanism of the production of these variations. The discontinuity follows from the existence of qualitative gaps between all specific chemical substances, such as those making up the system of genetic enzymes. The mechanism of production of variations is simply that of the initial production of any new chemical individual, *i. e.*, the fortuitous encounter of the appropriate molecules with the right relative orientations and at the correct speeds (*vide supra*). The "chance" nature of variation thus is made to depend upon that "molecular chaos" which is so very familiar to all physicists, but the implications of which for biology have thus far been largely neglected.

A moment's thought will show that, on the basis of the enzyme theory, variation should be *additive*, since an autocatalytic individual, once established, will tend automatically to maintain itself. The complete elimination of such individuals will occur only through the destruction of the entire germinal mosaic of which they form a part, an effect accomplished by natural selection unless the new enzyme is in harmony with functions which preserve the organism. It is very important to bear in mind that the catalytic complex which is supposed to underlie organic development and regulation has been determined in its nature by excessively exhaustive practical tests and, as a complex, by nothing else. It is therefore not surprising that the practical delicacy of the regulation which it actually subserves should be very great.

In other papers, I have discussed somewhat in detail the bearing of the enzyme theory upon the problem of the *origin of life*. On the basis provided by this theory, the

<sup>52</sup> See Kellogg, V. L., "Darwinism To-day," 1907.

origin of life can not be regarded as a catastrophic event; life depends upon an organized complex of selected catalytic material, and hence *some* life originates with each new, successful mutation. Of course, if we trace the process of the evolution of any given species back sufficiently far, we must eventually come to the *first mutation*, which would consist in the molecular production of an autocatalytic particle sustaining relations with its environment such as to make possible its continued growth and reproduction. I have used the name *protase* to stand for the "first enzyme" of the archebiotic process, but there is no particular reason for supposing that there was only one enzyme to which this name could apply.

There is considerable evidence that free autocatalytic enzymes exist in our biological universe even at the present day. Such an hypothesis would serve to account for the specific contagious diseases, such as measles, rabies, and smallpox, which have been demonstrated to possess "filterable viruses." The so-called Chlamydozoa probably fall in this class.

That the Chlamydozoa consist of free chromatin material is suggested by the late Professor Minchin, in his admirable paper on the evolution of the cell,<sup>53</sup> with the main outlines of which the enzyme theory would entirely agree. The single cell, and so-called simple protoplasm, must be regarded as the products of a detailed process of evolution, and hence can not form the ultimate explanatory units in biology. Next to the free autocatalytic particle, the simplest typical life-structure would consist of a single particle of this sort surrounded by an envelope of semi-liquid and chemically homogeneous substance with which it sustains a heterocatalytic relationship. The most primitive substance of this kind might be called *eoplasm*, to distinguish it from complex protoplasm, and the physical system made up of protase and eoplasm would represent a living cell in its most reduced form.

Minchin says, in the article referred to:<sup>54</sup>

<sup>53</sup> Minchin, E. A., "The Evolution of the Cell," AMERICAN NATURALIST (1916), 50, 5-39, 106-119.

<sup>54</sup> *Loc. cit.*, 35-36.

The biochemist renders inestimable services in elucidating the chemical mechanisms of living organisms but the problem of individuality and specific behavior, as manifested by living things, is beyond the scope of his science, at least at present. Such problems are essentially of distinctive vital nature and their treatment can not be brought satisfactorily into relation at the present time with the physico-chemical interactions of the substances composing the living body. It may be that this is but a temporary limitation of human knowledge prevailing in a certain historical epoch, and that in the future the chemist will be able to correlate the individuality of living beings with their chemico-physical properties, and so explain to us how living beings first came into existence; how, that is to say, a combination of chemical substances, each owing its characteristic properties to a definite molecular composition, can produce a living individual in which specific properties are associated with matter in a state of flux.

It is my contention that the enzyme theory of life satisfactorily meets these general requirements.

## V

To arrive at a proper estimate of the importance of a general theory such as the one discussed in the present paper, necessitates considerable reflection. The path of scientific progress is beset by the pitfalls of conservative empiricism, on the one hand, and by those of radical speculation, on the other. To the radicals the enzyme theory presents an aspect of *a priori* self-evidence; to the conservatives it seems to be a vague generalization with no particular or specific facts to support it, approximately on the same plane as the statement that "life is motion," which Driesch says is about as useful as the proposition that "Kant was a vertebrate." Regarding the general enzyme theory, the following opinion has been expressed to me privately by an eminent zoologist.

The idea . . . is a perfectly familiar one. The trouble comes when we attempt to make a specific application of this idea to a concrete problem, which is what science demands if a pure speculation is to become a valuable working hypothesis. For instance, how an autocatalytic molecule could produce the phenomena seen in the division of the chromosomes in the cell is by no means clear; nor is it clear why such molecules brought together during fertilization separate from each other at the maturation division. It is these specific questions that must first be answered, I think, before we can make much advance in

regard to the nature of the phenomena. . . . Of course, I realize that general ideas are always important for the development of science, only I think they should be advanced with caution and all attempts to make them appear as specific explanations should be avoided.

There are a number of principles of scientific methodology which have a bearing upon criticisms of this sort. In the first place such a statement as that "life is motion" would have value at a time when the connection between these two ideas had not been noted, or had been underemphasized to such an extent that eminent scientists were bemoaning the inability of the human mind to account for properties of life which the most superficial examination would show to be identical with those of motion. From my own point of view the proposition that "life is determined by specific catalysis" appears to be somewhat of the nature of a truism, indeed so much so that even if we had no direct evidence for the existence of enzyme action, we should be forced to invent the conception to account for the most general properties of living systems. It seems to me that this is exactly what a considerable number of biologists actually have done, and the only important error in their thinking lies in the application to the concept of such names as "biophore," "determinant," "unit character," "formative factor," "*Elementarorganism*," "*élan vital*," or "entelechy." This error, however, is fatal to progress, as it multiplies terminology and delays the synthesis of actual ideas which is the goal of scientific endeavor.

Furthermore, it is not true that the establishment of a general principle necessitates an examination of all of the concrete details of specific systems. If this were so, none of the fundamental laws of mechanics, such as the first and second laws of energetics or Hamilton's principle, would possess any rigidity, since they are derived from a study of what may be called the "entrance and exit" properties of mechanical systems, without reference to their exact contents. It is to be admitted, of course, that we can not rest content with this kind of knowledge, and that principles of this sort receive complete elucidation

tion only when the details of all systems are made clear, but the security of the principles themselves is affected scarcely at all by this analysis.

I do not claim that the enzyme theory of life possesses a general basis as adequate, for example, as that of the principle of least action. I do claim, however, that this is because the latter can be stated in terms of an exact mathematical formula, whereas the enzyme theory has to be given a qualitative description. The enzyme doctrine is supported at the present time by a considerable number of specific facts of cell chemistry, but it possesses a far more substantial bulwark in the general facts of vital function. Shall we deny that these facts are adequately established, or that they are important, or that they merit explanation? Shall we reject a definite physico-chemical conception which at one stroke explains the majority of the mass relationships of living matter, on the ground that the details of some special life-processes have not yet been described in terms of this conception? Or is it preferable to preserve the inexplication of these same generalities to furnish a basis for vitalism?

There are an indefinitely large number of ways in which the principle of the conservation of energy can be exemplified in special pieces of machinery, and there are just as many ways in which the principle of specific catalysis can operate. Instead of holding the energy principle in abeyance until we have seen how the action of a special mechanical system can be explained in terms of it, we usually assume it to be true, and shortly find the action in question very easy to understand. This would seem to be the only feasible method for employing any theoretical proposition, even if it is merely a novel working hypothesis. The trouble which arises in the attempt to apply the enzyme theory to specific problems is a normal result of the inertia of the human imagination, which does not immediately outline a plan for a machine to accomplish a definite purpose, even when it is provided with all of the principles of mechanics. Surely, however, the plan can never be developed if such principles are neglected.